Cancer Inquiry Protocol:

A Manual for Investigating Cancer Clusters in Missouri Communities

Missouri Department of Health and Senior Services
Division of Community and Public Health

May 2006

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Second Edition

Original Cancer Inquiry Procedures produced in 1984 by Jeannette Jackson-Thompson, MSPH, PhD.

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Ordering Information

This protocol is available on-line at www.dhss.mo.gov. For assistance, please call 573-522-2845 or write to the following address:

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- Missouri Cancer Registry
- University of Missouri-Columbia Center for Health Care Quality
- St. Louis University School of Public Health
- United States Agency for Toxic Substances and Disease Registry (ATSDR)

2005 – 2006

In 2005, a team of professionals within the Department's Division of Community and Public Health and the University of Missouri-Columbia began reviewing and editing the 1999 version. The May 2006 protocol document reflects updates to the cancer inquiry committee and investigative process.

The primary editors of this updated protocol were Deborah Markenson, MSRD, Administrator; Shumei Yun, MD, PhD, Chronic Disease Public Health Epidemiologist; Sherri G. Homan, RN, PhD, Public Health Epidemiologist; Victoria Fehrmann Warren, MS; Janette Candido, MD; Virginia Beatty; and Jeannette Jackson-Thompson, MSPH, PhD. Other department staff, as well as representatives from other agencies (below), supplied information and review comments:

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- Agency for Toxic Substances and Disease Registry
- Missouri Cancer Registry

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Table of Contents

Contents continued on next page.

Table of Contents (Cont.)

Preface

Addressing cancer cluster concerns through the Cancer Inquiry (CI) process is a core public health activity of the Missouri Department of Health and Senior Services (DHSS). DHSS follows a protocol to systematically guide an epidemiological response to an individual's concern related to cancer clusters in a Missouri community. The systematic approach to decision-making outlined in this protocol is based on the basic principles of epidemiological reasoning and causation. This protocol aims to assure a useful, efficient, cost effective, and scientifically sound CI process.

The first cancer cluster investigations in Missouri began in 1978 by DHSS. Addressing cancer cluster concerns through the CI process is part of DHSS' (then Missouri Department of Health*) core public health activities. The first formal procedure for cancer inquiries was written in 1984,[1] redesigned in 1999, and revised in this edition. In 2002, the Centers for Disease Control and Prevention (CDC), National Center for Environmental Health conducted a survey of state protocols for cancer cluster inquiry and investigation. The survey instrument was based on the 1990 CDC Guidelines for Investigating Clusters of Health Events and distributed to 56 states and territories.[2] The survey was designed to summarize the content and level of detail presented in each protocol. Missouri's protocol for cancer clusters with suspected environmental etiology scored the highest among the state protocols. The revisions in this document are designed to further align Missouri's protocol with the CDC guidelines.

* The Department's official name changed from the Missouri Department of Health to the Missouri Department of Health and Senior Services in 2002 when the Division of Senior Services was moved from the Missouri Department of Social Services. The Department's official name is now the Missouri Department of Health and Senior Services.

Abbreviations

Missouri Department of Health and Senior Services

BCCDC ..... Bureau of Cancer and Chronic Disease Control

BHI ..... Bureau of Health Informatics

BHP ..... Bureau of Health Promotion

BRFSS ..... Behavioral Risk Factor Surveillance System

CCC ..... Comprehensive Cancer Control Program

CDPNS ..... Section for Chronic Disease Prevention and Nutrition Services

DCEE ..... Section for Disease Control and Environmental Epidemiology

DHSS ..... Missouri Department of Health and Senior Services

MCR ..... Missouri Cancer Registry

MICA ..... Missouri Information for Community Assessment

OOE ..... Office of Epidemiology

PHPAS ..... Public Health Practice and Administrative Support Section

SMHM ..... Show Me Healthy Missourians

Other State Agencies

DNR ..... Missouri Department of Natural Resources

DOA ..... Missouri Department of Agriculture

Federal Agencies

ATSDR ..... Agency for Toxic Substances Disease Registry

CDC ..... Centers for Disease Control and Prevention

EPA ..... Environmental Protection Agency

NIOSH ..... National Institute of Occupational Safety and Health

NCHS ..... National Center for Health Statistics

OSHA ..... Occupational Safety and Health Administration

Professional Organizations

NAACCR ..... North American Association of Central Cancer Registries

Additional Abbreviations/Acronyms

CI ..... Cancer Inquiry

CII ..... Comparative Incidence Index

CMI ..... Comparative Mortality Index

CT ..... Census Tract

CTRs ..... Certified Tumor Registrars

DSIR ..... Directly Standardized Incidence Rate

DSMR ..... Directly Standardized Mortality Rate

ETI ..... Expected Time Interval

ICD-10 ..... International Statistical Classification of Diseases and Related Health Problems, 10th Revision

ICD-O-3 ..... International Classification of Diseases for Oncology, 3rd Edition

ISIR ..... Indirect Standardized Incidence Rate

ISMR ..... Indirect Standardized Mortality Rate

IRB ..... Institutional Review Board

MSA ..... Metropolitan Statistical Area

SEER ..... Surveillance, Epidemiology and End Results

SES ..... Socio-economic Status

SIR ..... Standardized Incidence Ratio

SMR ..... Standardized Mortality Ratio

ZIP ..... ZIP Code (Zoning Improvement Plan Code)

(Photo credit: Missouri Department of Tourism)

Introduction

Purpose

The purpose of the CI protocol is to assure a useful, cost effective, and scientifically sound process to investigate potential cancer cluster concerns. This protocol provides DHSS staff a systematic, scientific, and prompt way to respond to an individual's concerns about possible excess cancer in their communities, to provide the public with general information about cancer and dispel misconceptions, and to inform concerned individuals about what to expect from a cancer inquiry. The protocol is based upon the understanding that most cancer excesses or clusters identified are not related to environmental causes, but instead are due to normal random variation in cancer occurrences or are due to personal behaviors, genetic causes, or unknown factors. It is also based on the knowledge that the epidemiological investigations implemented to identify the source of the excess cancer often have little chance of determining a definitive cause.

Cancer Inquiry Process Overview

A large part of this process is to work with individuals or communities in exploring the nature of their cancer concern, providing health education on cancer and lifestyle risk factors, and, when appropriate, providing epidemiological information. DHSS staff, in consultation with the Chronic Disease Public Health Epidemiologist and the CI committee, works with communities in need of education. Staff or regional cancer coalition members may give educational presentations in locations with a cancer concern and may help to address the specific needs of that community. As part of this process, staff communicates with local public health agencies to coordinate, educate, and review cancer rates and risks.

The CI process focuses on determining if a perceived cluster(s) is real. If a true cluster is identified, then the CI staff will assist in the implementation of epidemiological studies, notify agencies responsible for remediation of the environmental hazard (if one exists), and educate residents in the area of concern regarding the risk and the response of state government and other agencies concerning cancer in their community. Rarely is it necessary to refer the identified environmental health hazard(s) for control or eradication.

DHSS also serves as a gateway for referral of environmental, regulatory, and health concerns. For example, if a community is found to have excess mortality from breast cancer, residents may be referred to the Show Me Healthy Missourians (SMHM) project to increase screening efforts. A complaint about pesticide use may be referred to the Missouri Department of Agriculture (DOA). Once an inquiry is complete, DHSS staff communicates the inquiry results concerning the perceived cancer excess to the inquirer and the community involved.

DHSS has created and maintains a CI database that stores information about each information request and CI. Examples of information contained within the database are demographics, geographic locations, and actions related to the CI.

Investigation Tools and Resources

The Department uses a cancer surveillance system to determine whether there is an increase in cancer incidence and mortality. Surveillance data can confirm increases in cancer incidence, or mortality, but it cannot definitively point to the cause of the increase. Questions related to cause are better addressed by systematic epidemiological studies.

Since the 1970s, when many state cancer registries were organized, many public health scientists and individuals hoped that the study of anecdotal observations of clusters of cancer in the community might lead to prevention of new cases by the discovery of specific causes of these cancers. Since then, hundreds of investigations have taken place throughout the country, mainly conducted by state, local, or federal agencies. With one or two exceptions involving childhood cancers, none of these

investigations have led to the identification of definitive causes of any of these possible clusters, even when a statistically elevated number of cancers in a geographic area could be documented.

The principal data source for the CI process is the Missouri Cancer Registry (MCR). Registry information is received from hospitals and other mandated reporting sources statewide and is used for case verification, case ascertainment, and incidence rate calculations. For the fifth year, MCR received Gold certification from the North American Association of Central Cancer Registries (NAACCR) with the 2003 data set submission. MCR data are not available or are very limited prior to 1985 since data submission from hospital-based registries to the MCR was voluntary at that time. In May of 1984, the Missouri General Assembly passed a bill to require hospital inpatient cancer reporting which was signed into law and became effective August 1984, (192.650 RSMo). Beginning in 1985 and through 1995, limited data became available as hospitals began submitting information. In May 1999, the Missouri General Assembly passed a bill expanding cancer reporting to include hospital outpatient settings, physician offices, pathology laboratories, ambulatory surgical centers, residential care facilities I and II, intermediate care facilities, skilled nursing facilities, and free-standing cancer clinics and treatment centers. The expanded reporting statute became effective August 28, 1999 (192.650-192.657 RSMo). CDC and the National Program of Cancer Registries developed national standards to ensure the completeness, timeliness, and quality of cancer registry data. Missouri has met, and continues to meet, these standards. In addition, Missouri's registry meets the highest standards of the NAACCR.

Other data sources include the Missouri Information for Community Assessment (MICA), death certificates, the Behavioral Risk Factor Surveillance System (BRFSS) and cancer case listings. MICA is an interactive system on DHSS' Web site that allows users to create tables or maps displaying data on public health topics such as deaths, hospitalizations, and cancer cases. The BRFSS collects risk behavior information from Missouri adult residents (age 18 or older) through a statewide telephone-based survey. DHSS mortality and hospital discharge data and data from special targeted surveys may also be evaluated. Current reference materials are also used in this process and include International Classification of Diseases and Related Health Problems 10th Revision [ICD-10][3], International Classification of Diseases for Oncology, 3rd Edition [ICD-O-3][4], Cancer Facts and Figures[5], etc.

Communication Plan

At every level of the inquiry process, CI staff, in consultation with the Chronic Disease Public Health Epidemiologist, prepares a report that contains recommendations for action. Should questions arise at any point throughout the process, DHSS' Office of General Council is consulted.

DHSS' Office of Public Information is notified of an inquiry being conducted and serves as a consultant and assists in implementing various communication methods as needed throughout the CI process.

The CI program staff meets quarterly, as needed, with the CI Committee to review active concerns and inquiries. The Committee guides staff actions in proceeding with the inquiry. Details of this process are further explained in the Committee Responsibility section of this document.

All correspondence with inquirers is copied to the Department's environmental public health unit, DHSS' Center for Local Public Health Services, the appropriate local public health agency, and any other agencies involved with the process.

Once an inquiry is complete, DHSS staff communicates the inquiry results concerning the perceived cancer excess to the inquirer and the community involved. This may be conveyed through public meetings, news releases, posting of the final report to DHSS' Web site, and by direct mail to the inquirer. The final report is posted on DHSS' Web site for public access. The Web site is also used to inform inquirers about the process, and for access by other agencies and researchers.

"Missouri has met, and continues to meet, these standards."

The CI process and staff assure all investigations and communications related to those investigations comply with DHSS' confidentiality policies and other applicable standards.

Comments related to this protocol document may be sent to the Department through the Web site.[6]

Protocol Summary

The protocol, a systematic approach, is used for decision-making based on the basic principles of epidemiological reasoning and causation. Upon initial contact by an individual, DHSS determines if it is a cancer information request or a concern. A concern becomes an inquiry when the individual requests the Cancer Patient Information Form be mailed or if DHSS elects to proceed to an inquiry. All cancer inquiries begin at level one of a four-level process (refer to Table 1). Each level uses epidemiological reasoning and/or statistical tests to determine if the inquiry should proceed to the next level.

"All communication is tracked until the individual is satisfied with the information provided…"

At each level the CI Committee reviews a written report, with recommendations for action. The Committee accepts, rejects, or revises the recommendations. Then, staff coordinates the implementation of approved recommendations.

Small Area Analysis

Small area or zip code level analysis may be conducted in Level 2 inquiries and for special studies. These analyses are conducted with approval from the Chronic Disease Prevention and Nutrition Services Administrator due to heightened community concern, when further exploration is warranted due to the impact on the community, the number of cases, or rarity of cancer type.

Table 1: **Missouri Cancer Inquiry Levels**

Level 1 – A Level 1 Inquiry consists of basic information gathering. The concerned individual helps gather the information. In addition, case verification is initiated and completed for cancer cases reported. Case ascertainment may be initiated. (Case ascertainment – searching cancer registry for active, suspended, and old cases from the area relevant to the time period.)

Level 2 – A Level 2 Inquiry involves additional research into specific risk factor(s) for the cancer of concern. Case ascertainment is completed. In addition, epidemiological analytical methods and assessment, including statistical testing, are used to determine if there is an actual cancer cluster.

Level 3 – At Level 3 Inquiry, case verification and ascertainment are completed. Additional research into the environmental concerns, the specific risk factors for the concern, and more detailed application of epidemiological methods and assessment are conducted.

Level 4 – A Level 4 Inquiry is an advanced, structured, case investigation. This involves conducting a feasibility study to determine if an analytical epidemiological study and/or environmental assessments study is needed. If such studies are warranted, the study design and implementation begins and continues until there is resolution.

Staff

The CI Program is staffed by means of collaboration between various offices within DHSS. The CI Program is located in the Division of Community and Public Health (DCPH), Section for Chronic Disease Prevention and Nutrition Services (CDPNS), Bureau of Cancer and Chronic Disease Control (BCCDC).The Chief of BCCDC serves as the Chair to the CI Committee. In addition, this position oversees the work of the CI Program, convenes meetings of the CI Committee, and is responsible for the media, legislators, and policy regarding the direction of the CI Program.

The Comprehensive Cancer Control Program (CCC) Manager within the BCCDC coordinates and facilitates contacts; serves as liaison with collaborating agencies; provides direction and coordination of educational efforts; facilitates an environmental threat response; and establishes and maintains communication channels with residents, and other members of the public involved in cancer inquiries. In addition, the manager updates the BCCDC Chief regarding all new inquiries, speaks for the Department regarding these inquiries, and directs daily operations of the CI Program in collaboration with the epidemiology and research staff.

The BCCDC also provides a main point of contact for all cancer inquiries. This staff person gathers information from the concerned individual(s) and begins the process of investigation if the individual seeks to determine if the environment is the cause. All communication is tracked until the individual is satisfied with the information provided or the investigation is complete and resolved.

The Bureau staff work with research and epidemiology staff in the Department who provide epidemiological consultation on cancer cluster occurrences. This consultation assures the use of epidemiological criteria and reasoning as well as the application of a systematic method(s) to evaluate cancer clusters, supervision of the process of case verification and ascertainment, design and implementation of feasibility and etiological studies, and final reporting with recommendations to the CI Program and committee.

Committee Appointees

The CI Committee consists of epidemiologists, environmental specialists, health educators, statisticians, and other specialists who oversee the CI process. Committee representation (required membership) comes from the following organizations:

- Chair – Chief, BCCDC; DHSS – chairs CI Committee meetings and provides program oversight.
- CCC Manager – DHSS – works with community coalitions to help communities take action to improve health and to reduce cancer risks, and provides education on cancer prevention and control.
- Chronic Disease Prevention and Nutrition Services Administrator – DHSS – Participates in the CI Committee review process and coordinates with other DHSS sections and other agencies as needed.

- Chronic Disease Public Health Epidemiologist – DHSS – oversees research methodology, supervises case verification and ascertainment, and reviews case listings and rate calculations. Also provides summary and statistical information about cancer cases.
- Cancer Epidemiology Specialist/Research Analyst III – DHSS – requests, obtains, and analyzes case ascertainment and case verification. In addition, assists and works in collaboration with the Chronic Disease Public Health Epidemiologist to conduct necessary research.
- Missouri Cancer Registry Operations Representative – performs case verification and may assist with case ascertainment.
- Environmental Specialist – DHSS – provides technical assistance to the CI Program concerning the environmental aspects of cancer inquiries. This may include information on hazardous waste sites and information on hazardous substances, including dioxin and radiation. This representative coordinates with other environmental agencies including, but not limited to, the Federal Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). A significant proportion of cancer inquiries are initially received by environmental health staff and then referred to the CI Program. The Section for Disease Control and Environmental Epidemiology (DCEE) designates an environmental specialist to serve as the primary contact for the CI Program.
- The Missouri Department of Natural Resources (DNR) Representative – (required membership) – provides information concerning regulatory issues when immediate environmental health hazards are present. DNR also assists by providing reports on environmental issues such as water and air quality. One member of DNR is designated to be the Department's liaison with the CI Committee.
- Research Analyst – DHSS – conducts additional analysis of mortality data used in the cancer inquiry, and may also provide a listing of people whose cause of death was listed as some form of cancer under investigation, which is used in case ascertainment. The Bureau of Health Informatics (BHI) designates a research analyst to serve as the primary contact for the CI Program.
- Center for Local Public Health Services Representative – DHSS – serves as the CI Program's liaison with the local public health agencies. This Center serves as a means for information to travel from the CI Program to the local level and for feedback from the local level to the CI Program.
- Missouri State Tumor Registrars Association (MoSTRA) Representative – provides input into the committee's review on cancer inquiries and can assist with the process for rapid case ascertainment, as needed, when a Level 2 or Level 3 Inquiry is being conducted. The representative shares information with MoSTRA regarding the CI process and linkage and use of the MCR data.

The committee conducts reviews of cancer concerns and determines how to proceed.

The CI Committee may consult with a variety of other organizations or groups to solicit their expertise and input into a CI. Representation may include an individual or individuals from the following organizations:

- Local Public Health Agencies – may become involved when an inquiry occurs in their service area and there is significant public concern. These agencies are invited to all meetings that concern a cancer inquiry issue in their jurisdiction.
- Public Information Specialist – DHSS – serves as a consultant for cancer concerns and inquiries. A member of the DHSS public information team also assists with town hall meetings, press releases, and other communiqué with residents, media groups, etc., surrounding a cancer concern or inquiry.
- General Counsel – DHSS – serves as a consultant for cancer concerns and inquiries on an as needed basis.
- Certified Tumor Registrar – depending on the case being evaluated, the DHSS staff or CI committee may consult with a Certified Tumor Registrar from the Missouri Cancer Registry.
- Technical Assistance – sought as needed from the Office of Public Information, Office of Epidemiology, Cancer Registry Coordinator, Certified Tumor Registrar, CDC, ATSDR, EPA, and others.

Committee Responsibility

The CI Committee reviews each report and may recommend changes. The CI Committee conducts reviews of cancer concerns and inquiries and determines how to proceed. All members receive a summary report the day of the committee meeting outlining the work and research that has been done in response to concerns and inquiries. Committee meetings are held quarterly in accordance with and are subject to the provisions of the Missouri Open Meeting Law (610.021 Revised Statutes of Missouri), also known as the Sunshine Law. However, any discussion of specific cases is closed to the public. All DHSS policies are strictly followed concerning the release of information to the public.

Committee members review the report and a vote is taken at the meeting to determine whether to close the inquiry or to recommend it for further investigation. When an inquiry is closed, the CCC Manager sends a letter and final report to the inquirer. (Refer to Appendix A for a sample report outline.) The report includes all of the information gathered and the findings of the CI Committee. If additional information is needed from the inquirer at this stage, a request for such information is included in the letter

that accompanies the report. If a request is made to an outside agency for help, the CI staff informs the inquirer and explains the next steps.

Initiation of the Cancer Inquiry Process

The process begins with an initial contact from an individual, a health sector representative (e.g., local public health administrator, physician, nurse, certified tumor registrar, etc.), a government agency or official (e.g., the EPA, a state legislator), or a CI Committee member regarding perceived excess cancer cases or cancer-related deaths in a specific county, community, neighborhood, or other defined geographical area or sub-population. Contact is usually made by phone, but can also be made by letter, e-mail, or through the DHSS and CDC Web sites. All calls and incoming messages are referred to the CCC Program manager. The next several paragraphs define what is classified as a cancer information request, a cancer concern, and a CI.

Cancer Information Request

If the initial contact is about a personal cancer concern, and not the occurrence of excess cancer within the caller's community, it is classified as an **information request**. An example would be a mother calling for information on Burkitt's lymphoma because her son was recently diagnosed with this type of cancer. She is not concerned about excess occurrences of cancer in the community. The CI staff will answer the mother's questions and send information as requested.

Cancer Concern

If the initial contact is about cancer within their community or workplace it is a classified as a concern. If, however, after receiving information that allays their concern, a Level 1 Inquiry is not pursued, i.e., distribution of the Cancer Patient Information Form, it remains a concern.

1. **Cancer Concern – Occupational (Worksite)**: An inquiry may involve issues that are of concern to other local, state, or federal agencies, such as DNR, DOA, etc. When this occurs, the issue is referred to the appropriate agency. Because cancer incidence data submitted to, and maintained by MCR, are entered according to residence, this does not easily allow researchers to track occupational clusters. If the **concern** centers on a worksite, it may be referred to either the National Institute for Occupational Safety and Health (NIOSH) or to the Occupational Safety and Health Agency (OSHA) for investigation. Because NIOSH's procedures require that an employee or manager submit the complaint, the application for the process will be included in a letter to the inquirer by the appropriate federal agency. However, the CI Program can refer concerns directly to OSHA if there is evidence that a public health threat may be present. In either instance, DHSS will assist in any research conducted as a result of the referral.
2. **Cancer Concern – Community:** Initial contact is about a suspected or apparent excess of cancer in a community that they can define along with a possible cause. After discussion with the CI program staff, and information provided, the individual(s) better understands cancer and its causes and elects not to pursue the Cancer Patient Information Forms. Example: An individual has concerns about the possible excess of cancer cases in his area of residence. He states that he knew of two children diagnosed with brain cancers within less than one mile from each other and, that he has heard of several cancer cases in the area. He wants to know if the well water is possibly causing the cancer since most of the individuals he knows are in the rural area and drink well water. The CI contact person looked into MICA for incidence and mortality data for the cancer of concern and found no significant increase in rates. Following a discussion and relaying information to the individual, the individual decided not to pursue the CI process. This example is classified as a **concern**. However, the Department may elect to proceed to an inquiry even if the individual chooses not to pursue.
3. **Requests Related to Previous Inquiries –** if the individual or DHSS is concerned about a geographical area studied in another inquiry, the final report from that inquiry is sent to the individual, and the inquiry is classified as a **concern**.

The CCC Manager will retrieve the mortality and incidence data from MICA to determine if the cancer of concern is statistically higher in the county of interest. Data is extracted only for the specific cancer of concern. The CCC Program Manager will work with the epidemiology specialists if deemed necessary; if the county rate is statistically higher than state rate or if the CCC Manager and/or inquirer needs additional information. No written report is generated. Appendix B is a sample letter that is sent to an individual with a cancer concern when follow-up is requested. Appendix C depicts information completed within the electronic database.

Cancer Inquiry

If, after the initial interview and discussion with the individual, the individual wants to pursue the concern, the concern is now moved to a Level 1 **Inquiry** and the Cancer Patient Information Forms are mailed to the individual for distribution. The database is updated to reflect this change. All letters, actions, reports, etc., are recorded in the database.

"Contact is usually made by phone, but can also be made by letter, e-mail, or through DHSS and CDC Web sites."

(Photo credit: Missouri Department of Tourism)

Protocol

Criteria to move to level 1

The following conditions **must be** met in order to consider pursuing a Level 1 Inquiry:

A. After the initial interview and discussion with the individual, the individual wants to pursue the concern.
B. Cancer Patient Information Forms are mailed to the inquirer and returned by cancer patients.

Or

A special study **may also be** pursued without the above conditions being met: **If** DHSS administration finds that a heightened community concern is present or the potential impact on the community (e.g., high incidence or mortality) warrants such an investigation.

Level 1 Process

Phase I:

During the initial contact, the CCC Program manager determines whether the call is an information request or a concern that proceeds to an inquiry through basic information gathered during a telephone interview with the inquirer. The interview usually lasts about an hour.

Appendix C shows the data collected. Information collected includes inquirer information, i.e., name, address, telephone number; basic information about the concern; general information about the number of cases in the geographical area in question; the cancer type(s) and site(s) involved; and suspected environmental exposures or hazards that may be contributing to the perceived excess. Once the initial questions are complete, the remainder of the interview focuses on cancer education; information about the CI Program; the prevalence of risk factors; screening opportunities for cancer; and the next steps of the inquiry process. The information collected during the interview is entered into the database.

Note: The inquirer's identifying information is always kept confidential, although other information gathered is shared.

All correspondence with inquirers is copied to the Department's environmental public health unit, DHSS' Center for Local Public Health Services, the appropriate local public health agency, and any other involved parties. In this correspondence, the name of the inquirer is always kept confidential.

After the interview, the CCC Program Manager assigns the concern a case number. This case number consists of the year in which the first contact occurs and a number assigned in order (e.g., the third inquiry received in 2005 would be 05-003.) The Initial Response Letter (Appendix B) is prepared and sent to the inquirer along with a packet of other relevant information within 10 days:

- *What is Cancer* from the Agency for Toxic Substances Disease Registry (ATSDR),
- *Burden of Cancer in Missouri* (Booklet),
- Mortality and/or incidence rates from MICA (if applicable),
- MICA web address (www.dhss.mo.gov/MICA),
- American Cancer Society web address (www.cancer.org/docroot/home/index.asp),
- Cancer Information Service web address (http://cis.nci.nih.gov), and
- Any other information specific to the inquiry.

The packet also includes copies of the Cancer Patient Information Form (Appendix D). This form is explained to the inquirer during the initial telephone interview. The inquirer has approximately two (2) weeks to distribute the forms to individuals with cancer and to explain the purpose of the inquiry. The inquirer asks the individuals with cancer to return the forms to DHSS within four (4) weeks. Patients are asked to mail the forms directly to DHSS in order to maintain their confidentiality. Should questions arise at any point throughout the process, DHSS general legal counsel is consulted.

An inquirer who needs more time may contact the CCC Program Manager to request the additional time. If forms are not received in six (6) weeks, a certified, return-receipt letter (Appendix E – Initial No Response Letter) is sent to the inquirer,

explaining that the inquiry will be closed if the CI Program does not hear from the inquirer within two (2) weeks. If the inquirer still does not respond, or if patient forms are not received, the inquiry is considered closed and a certified, return-receipt letter stating such is sent to the inquirer (Appendix F) explaining the outcome.

Phase II:

> **Case verification** is the process of verifying the accuracy of information on each case submitted using MCR data.
>
> **Case ascertainment** involves the identification of additional cases through an active search of existing cancer databases.

Phase II of the Level 1 process begins once the Cancer Patient Information Form(s) are returned. The CI staff (support staff) sends a Confirmation Letter (Appendix G) that explains the next steps in the CI process and informs the inquirer when the next meeting of the CI Committee will be held. The concerned individual may attend the "open" portion of the meeting. A copy of the confirmation letter is also sent to DHSS' Office of Public Information to notify administration that a CI has begun. The epidemiology specialist submits the Cancer Patient Information Form to the MCR. Case verification is conducted by MCR in all cases where the Cancer Patient Information Form(s) are received. Information obtained through case verification includes the site, histology and stage of the cancer at diagnosis, date of diagnosis, gender, race, smoking status, occupation, date of birth, and address at diagnosis. Doctors' records, hospital records, and/or death data are alternative sources for case verification. Cases not confirmed by a medically reliable source are excluded from data analysis. Case ascertainment may also start in Level 1. Then CI Program staff, in consultation with the Chronic Disease Public Health Epidemiologist and the designated epidemiology staff review the forms and develop a preliminary report (Appendix A). The Committee determines whether the inquiry meets the criteria to conduct further research and if it should move to a Level 2 Inquiry.

Criteria to move to Level 2:

The following conditions must be met in order to consider pursuing a Level 2 Inquiry:

A. Cancer Patient Information Forms are returned.

B. A definable type of cancer is reported.

C. Case verification is completed. When the case verification is complete, a Level 1 preliminary report is reviewed by the CI Committee, which then makes a recommendation to DHSS whether the case warrants pursuing the Level 2 Inquiry. If it is determined there is no potential cancer cluster in the community, the inquiry is closed, and a letter is sent to the inquirer informing them of this finding and closure.

D. The type of cancer or types of cancer being reported have a common suspected risk factor(s).

E. At least one specific environmental or occupational cause (exposure) is suggested for this excess (e.g., dioxin, radiation, asbestos).

F. A preliminary literature review is conducted and there is no evidence of common behavioral or other risk factors with strong, well-proven relationships to the identified cancer (e.g., between smoking and lung cancer; between polyvinyl exposure in occupational settings and angiosarcoma [cancer of the blood vessels]; and between asbestos and mesothelioma [a type of lung cancer]). In many situations, a literature search will not support the plausibility of the association between the exposure and the cancer of concern. However, it is always possible that a new and not yet studied association, including a different pathway for exposure, may exist.

G. There is a plausible scenario for the patients to have come into contact with a suspected cause of the cancer(s). For most cancer sites, if cancer latency is not known, a minimum of ten years' residency in the study area or exposure in the occupational setting is necessary for the suspected association to be considered plausible. Childhood cancers may have a shorter latency period.

In addition, at least two (2) of the following characteristics **must also** be present:

A. A common type of cancer is occurring in an unexpected age group.

B. The cancer of interest is rare.

C. The suspected exposure is plausibly linked to the cancer(s) of concern, based on the available knowledge base and research.

D. If the cancer latency in relation to a particular exposure is known, there is a reasonable match between the estimated time individuals with cancer (cases) were exposed and this latency. If the cluster is in a community setting, the time a case has been exposed is estimated by the time the case lived in the area of concern and the time exposure was first established. If the cluster is in an occupational setting, the time of exposure is estimated by the time the case was employed and when exposure was first established.

"Once the initial questions are complete, the remainder of the interview focuses on cancer education…"

If the CI Program Cancer Patient Information Forms are not returned and if the inquirer makes no further contact within the designated time frame, there are two (2) instances in which the CI Program can still proceed to a Level 2 Inquiry:

- The Chronic Disease Public Health Epidemiologist, in collaboration with the CI staff, concludes that there is enough information to indicate a potential public health risk.
- A situation involves heightened community concern and DHSS administration determines such an action is warranted.

A letter is sent to the inquirer to notify them if the inquiry is closed or if DHSS is proceeding to the next level.

"...the Committee determines if there is a potential cancer cluster in the community."

Level 2 Process

A Level 2 Inquiry involves additional research into specific risk factor(s) for the cancer of concern. Case verification is complete. In addition, the application of epidemiological analytical methods and assessment, including statistical testing, are used to determine if there is an actual cancer cluster. The epidemiological investigation by the Chronic Disease Public Health Epidemiologist and the epidemiology specialist(s) determines if there is a potential cluster of the cancer or cancers of concern. The analytical research conducted includes:

A. Comprehensive literature search for additional information about risk factors and review of BRFSS and county-level data.

B. If case ascertainment is not initiated in Level 1, it is initiated in Level 2 and consists of searching existing databases for cases of the cancer(s) of concern in the geographic location beyond those submitted through the Cancer Patient Information Forms.

C. Calculations and statistical testing by geographical area, time periods, and major demographic groups.

A Level 2 preliminary report is prepared and presented to the CI committee. After reviewing the recommendations and other relevant data and information collected from Levels 1 and 2, the CI Committee determines if there is a potential cancer cluster in the community. If there is not a cancer cluster, the inquiry is closed and a letter is sent notifying the inquirer. The letter is drafted in conjunction with the CI committee and forwarded to the inquirer and the local public health agency through certified mail and a return receipt is requested.

Criteria to move to Level 3

If clustering of cancer occurrence is supported by the Level 2 research, the following conditions **must be** met before moving to a Level 3 Inquiry:

A. All conditions and characteristics set forth as criteria for moving to a Level 2 Inquiry are met.

B. Case ascertainment is initiated and completed.

C. At least five (5) cases of one type or related types of adult cancer, or at least three (3) cases of one type or related types of childhood cancer per sub-population of interest (age group within gender and race) in the study area.

D. Statistical calculations indicate the possibility of a cancer cluster. Supportive findings include: statistical results are consistent across tests (congruency among spatial clustering testing and congruency among temporal clustering testing), and are robust to statistical flaws intrinsic in the tests.

E. There must be an exposed population large enough and well-defined enough to conduct a more detailed analytical study with further classification of sub-populations. The Chronic Disease Public Health Epidemiologist oversees research methodology.

If the CI Committee determines there is a possible clustering of cancer occurrence or sufficient evidence, the inquiry moves to Level 3. A letter is sent to the inquirer explaining the reason for proceeding with additional analyses, while providing any other relevant findings. The letter is drafted in conjunction with the CI committee and forwarded to the inquirer and the local public health agency through certified mail and a return receipt is requested.

A Level 3 Inquiry **may also be** pursued without the above conditions being met **if**:

- In the opinion of the CI Committee, other information or data analysis of the inquiry justify further study of the association between the suspected environmental exposure and the cancer of interest, **or**
- The CI Committee and DHSS administration find that a heightened community concern is still present surrounding the inquiry.

A Level 3 Inquiry is rare.

Level 3 Process

During a Level 3 Inquiry, a more detailed and in-depth epidemiological evaluation is conducted by DHSS and other state and/or federal agencies. The exact research may vary, but may include any or all of the following:

- Literature searches for additional information about risk factors;
- Rapid case ascertainment that encompasses a wider geographical area, additional time periods, and/or searches of other databases;
- Data analysis incorporating either further defined demographic sub-groups, a wider geographical area, or additional time periods;
- Additional statistical testing for assessing consistency in defining the cluster;
- Collection of additional information on the environmental concern, which may include cooperation with other agencies or departments;
- Other information relevant to the specific inquiry.

Once the Level 3 Inquiry research and Level 3 preliminary report are completed, data are presented to the CI Committee. The Committee reviews the findings and makes recommendations. A Level 4 Inquiry is pursued **if** specific conditions are met.

Criteria to move to Level 4

It is recommended that a Level 4 Inquiry be pursued **ONLY if** the following conditions are identified at the end of a Level 3 Inquiry:

A. All conditions and characteristics set forth as criteria for moving to Levels 2 and 3 are met.

B. There is a population large and well-defined enough to conduct a more detailed analytical study.

C. The epidemiological investigation and statistical testing clearly indicate clustering.

Unequivocal clustering is indicated by:

A. Additional calculations using related alternative time and space clustering statistics that are consistent with previous statistics.

B. Additional calculations for time and space clustering find a highly statistically significant increase of cancer incidence over one time period (time clustering) or significant differential between geographical areas ($p \leq 0.001$; one-sided).

C. Additional calculations for time clustering find a statistically significant increase ($p \leq 0.025$; one-sided) over two consecutive time periods.

If clustering is clearly determined at the Level 3 Inquiry, an environmental assessment may be initiated or completed before proceeding to Level 4. The DHSS environmental epidemiology staff should make this determination and organize the necessary action. This assessment may be conducted initially by DNR with the help of federal environmental agencies. If a current exposure or an environmental or occupational health hazard is identified, efforts are initiated to control or prevent further exposure.

A Level 4 Inquiry **may be pursued** without the above conditions being met **if**:

- In the opinion of the CI Committee, other identified aspects of the inquiry warrant the pursuit of an analytical epidemiological study of the association between the suspected environmental exposure and the cancer of interest, **or**
- The CI Committee and the administration of DHSS conclude that a heightened community concern is still present surrounding the inquiry.

Level 4 Process

A Level 4 Inquiry begins with an environmental assessment (if not previously conducted) that is followed by an initial feasibility study and the design of an analytical study (i.e., epidemiological investigation). At this level, if an analytical study is feasible, additional case ascertainment will be pursued and completed. The investigators also evaluate the feasibility of an analytical study when either the suspected exposure or cancer occurrence is rare. The critical elements in determining the feasibility of an analytical study are:

- Additional rapid case ascertainment is completed through community research,
- Identification of the requisite minimum number of cases in an identifiable study population of sufficient size, and
- The ability to measure environmental exposure both at the community and at the individual level.

Scientific Support for Investigation

DHSS may request outside agencies, such as CDC and ATSDR, to participate in the feasibility study, environmental exposure assessment, or the design and implementation of the analytical study. This generally occurs when a cancer cluster (excess cancer cases) has been found and the resources needed to conduct further research are beyond the capacity of DHSS.

When an analytical epidemiological study is recommended, it is likely to be conducted by another agency or a research group in an academic setting, with the help of the CI Program and the epidemiology staff. Outside researchers must submit a research plan and receive DHSS Institutional Review Board (IRB) approval before confidential data are released.

Once the study is completed a final report is written, approved by the CI Committee, shared with the inquirer and the local public health agency, and is posted on DHSS' Web site. The report is sent to the inquirer and local public health agency through certified mail and a return receipt is requested.

If an analytical study is not feasible, the inquiry is closed and the inquirer is notified. The letter is drafted in conjunction with the CI committee and forwarded to the inquirer and the local public health agency through certified mail and a return receipt is requested.

(Photo credit: Missouri Department of Tourism)

Analytical Methods

Epidemiological Evaluation of Cancer Clustering

The evaluation of cancer clusters is not different from other epidemiological evaluations with respect to the use of epidemiological reasoning and principles. These principles are used to guide DHSS staff in every step of the inquiry process in order to determine if a cancer cluster exists and if there is a possible cause for that cluster that needs to be examined in an epidemiological investigation. In the same manner of analytical studies, the consistent reliability, biological plausibility (likelihood), and dose-response of the suspected disease and environmental exposure association should be evaluated.

The criteria for deciding whether to initiate additional analytical work at each level of the CI process should address a number of issues: the case and exposure definition (ill-defined or well-defined); length of time (i.e., latency period) between initial exposure and disease diagnosis; plausibility of the exposure pathway; and confounding or other possible explanations for the observed increased incidence and mortality. After conclusion of a Level 3 Inquiry, the feasibility of an epidemiological investigation (Level 4) is questioned **if** the:

- number of cases is small,
- cancer occurrence is rare,
- environmental exposure is rare,
- cancer occurrence and environmental exposure are both rare, or
- ability to measure exposure at both the community and the individual level is weak.

This inquiry process is conducted with an understanding of the limitations for establishing causal links using either surveillance or individual level data that is incomplete. The evaluation of cancer clusters involves the use of investigative methods capable of generating, not testing, hypotheses.

In addition, the limitations of statistical testing in epidemiological settings are considered. Statistical testing, at its best, can only assist causal reasoning. The "significance" of the epidemiological causality principles and the "significance" of patterns and trends of health events and their implications for public health far outweigh the "significance" of a *p-value* (probability of a type-I error).[7]

The *p-value* is an ambiguous measure that is both a function of the uncertainty (precision of the measure) of observing the effect being evaluated and the magnitude of the effect. Given a large enough sample, a "significant" effect, or an association, can be demonstrated even when it is small and with little epidemiological or public health significance. For this reason, it is good epidemiology to separate out the two (2) components of an association in a meaningful way when presenting epidemiological results. For example, rate ratios and standard error of the ratio with subsequent calculation of a 95% confidence interval on the ratio will do exactly that. The rates and rate ratios provide information on the effect and its magnitude; the standard error provides information on the precision of the estimate.

- As an illustration for this discussion, consider the following scenario: A call is received from a concerned individual about a cluster of six (6) cancer cases in one (1) year in a single, well-defined, neighborhood (e.g., a city block). The cancer cases reported included breast, colon, lung, uterine, skin, and prostate cancer among individuals aged 65 and older at the time of diagnosis. Using the epidemiological reasoning and criteria for causation, these cases could not be environmentally related, despite the demonstration of a statistically significant cluster. The reason is the different types of cancer and the different risks for the cancers, including those that are related to behavior.
- As a second illustration, consider a call that is received from a concerned individual about a cluster of 16 cancer cases in one (1) year in a single larger neighborhood (e.g., a zip code ~ ZIP) and possible dumping of hazardous material by an industrial plant. The cases reported are all lymphatic cancer among individuals aged 65 and older at the time of

diagnosis. The difference between observed cases and expected cases is not significant and could have occurred by chance. However, using epidemiological reasoning and criteria for causation, these cases could be environmentally related, despite the demonstration of a statistically non-significant cluster. The reason has to do with similar types of cancer that may share similar risks, including behavior and genetic factors.

Study Area

For all levels of a CI, the study area is the smallest identifiable geographical area from which cases arise that allows for reliable rate calculations and statistical testing. The most recent population database (US Census) and annual updated estimates from DHSS Public Health Practice and Administrative Support Section (PHPAS) are used. The study area is defined by one or more of the following; county, ZIP, census tract (CT), Metropolitan Statistical Area (MSA), or city.

For the purpose of rate calculation, a city and a MSA may, or may not, overlap the same geographical area. For directly adjusted rates, if a MSA contains a city with at least 50,000 inhabitants and a sufficient number of cases arise from the city, calculations will be implemented using the city as the study area.[8] However, if a sufficient number of cases arise from a city with a population smaller than 50,000, but within a defined MSA that meets the above conditions, the MSA will be defined as the study area. For indirectly adjusted rates, the same rationale is used with an area population of at least 10,000.[9] Calculations for rates and statistical testing for cancer cases that arise from other geopolitical areas (e.g., ZIP or county) for which both observed cancer cases and population size are available, and appropriate, will be used as the study area.

Other possible study areas include schools and occupational settings for which both the total number of cases and the total population size can be reported and later verified and ascertained. Typically, areas larger than, and contiguous to, the study area should be used as a comparison during a cancer cluster investigation. It is possible that after case verification (Level 1 Inquiry) and case ascertainment (Level 2 Inquiry), the boundaries of the study area may be modified.

Study Period

The study period usually corresponds to the identified dates of incident or deceased cases reported on the CI Inquiry Program Response and Cancer Patient Information Forms for Level 2 and above inquiries. For a Level 3 Inquiry, the study period may correspond to verified and ascertained incident or deceased cases.

In an inquiry situation where an insufficient number of cases is identified but an inquiry is perceived as necessary, DHSS administration and the CI Committee, in consultation with the Chronic Disease Public Health Epidemiologist, may decide to pursue further research. In this situation, additional years of incidence and mortality data, if available, are used beyond the years indicated by the CI Initial Report Form and the Cancer Patient Information Forms.

In a situation when the evaluation of evidence for clustering at Level 2, Level 3, or Level 4 is not statistically significant, but there is plausibility for establishing a cluster, additional years of data may be used to increase the statistical power of the analysis.

In either of these two situations, the ideal denominator for rate calculations is that of the population estimates of corresponding years from which verified and ascertained cases arise.[10] In practice, depending on the definition of the study area, if population-based data by demographic groups is not available, the population estimates of the last US Census are used for all yearly and aggregate rate estimates. A historical series of either incident or deceased cases in a study area that are available in DHSS databases may also be used to evaluate randomness of occurrence over time and space.

"...these cases could be environmentally related."

Population

A choice of study (population at risk or index population) and comparison populations for statistical calculations, including area and period, as well as sub-populations (gender, race and age groups), will be dictated by the availability of population-based data.

Population-based data used for rate calculation may include the most current US Census, the most current Missouri Census, or updated US or Missouri inter-census population estimates by gender, race and age group that are provided by the National Center for Health Statistics (NCHS) and BHI, respectively. For standard US and Missouri comparison incidence rates, population-based incidence rates are the Surveillance, Epidemiology, and End Results (SEER) Program, the NAACCR, the U.S. Cancer Statistics (UCSC), or the MCR, respectively. The source depends upon the time period involved.

The comparison population during the period of concern for directly standardized incidence and mortality ratios will be the US and Missouri populations for incidence (SEER and MCR incidence estimates) and Missouri mortality (BHI mortality estimates), respectively. The US 2000 Census Standard Population is the standard used for direct age-adjustment of rates. The comparison populations from which standard rates are used for indirect age-adjustment of rates during the same period of concern are the

populations of either the US or Missouri. The study population is the index population as defined using geographical and time period criteria described above.

Ideally, at a Level 2 Inquiry, sub-population analysis should include classification of cancer occurrence and death by gender and race, regardless of the choice of study area and period. At Level 3 and Level 4 Inquiries, further classification of rates into age-specific groups is warranted as is classification by occupation and smoking status if data are available. Childhood cancers are the exception to this classification of sub-populations; no further separation by gender is attempted. Also, because index (study) population observed rates and counts are compared to rates expected from a comparison population, the choice of the study population is made only after identification of a comparable population.

Cancer Sites

Data analyses are completed using a variety of software programs including SAS, SPSS, and Epidemiology Information.

Only primary sites are studied. For example, if the inquiry is focused on possible excess brain cancer, cases will be included only if the brain is the primary site. Cases where the cancer has metastasized (i.e., spread) to the brain from a different primary site (e.g., lung, breast, etc.) will be excluded from analyses. Primary sites are identified using ICD-O-3 codes for incidence cases and ICD-10 codes for cases identified through death files.

For initiation of Level 2 Inquiry calculations, it may be assumed that the case notification by the individual and others submitting Cancer Patient Information Forms is adequate. Whenever possible, calculations are made using both this information and any additional cases verified by MCR in the study area. For Level 3 and Level 4 Inquiries, thorough case ascertainment of diagnosis will determine accuracy of reported sites.

If the individual's report involves more than one site, attempts will be made to calculate incidence and mortality statistics for all sites involved during a Level 2 or Level 3 Inquiry. If only one cancer site is involved, then incidence and mortality statistics are calculated for this site and for "all cancer" by the same sub-populations as described under the population section. If the inquiry concerns a childhood cancer, the SEER pediatric major cancer group that includes the cancer of interest, will be used instead.[10]

Case Verification and Ascertainment

Case Verification

For a Level 2 Inquiry, the information from the inquirer and the Cancer Patient Information Form(s) is verified for accuracy of diagnosis (site, histology and stage), date of diagnosis, address of patient or decedent at time of diagnosis, demographic factors (sex, race, date of birth, marital status, occupation, etc.), and risk factors (smoking history and toxic exposure, if available). Primary verification sources include the MCR database as well as mortality data and possibly other sources such as hospital discharge data, specific program data and records from physician offices, clinics, path labs, etc.

Case Ascertainment

Case ascertainment may be initiated in Level 1 or Level 2. Rapid case ascertainment may be needed to obtain information on recently diagnosed cases in Level 3. Usually it is conducted if the Chronic Disease Public Health Epidemiologist and/or the CI Committee make the recommendation. Case ascertainment involves an active search for additional cases in the study area by CI staff and MCR staff. It also includes double-checking for inconsistencies in: primary site, date of diagnosis, date of death (if applicable), and additional verification of address, demographics, time residing in the study area, occupational activities, and geocoding for precise determination of the geopolitical study area.

The search for additional cases and crosschecking of case information is implemented by certified tumor registrars (CTRs) from MCR in collaboration with the registrars at reporting facilities in the study and surrounding areas. MCR staff also matches cases on the Cancer Patient Information Forms with cases in the MCR, hospital discharge, and mortality databases. The geocoding is obtained by utilizing a geographical software program (ArcView) and a census database to match addresses of cases submitted on the Cancer Patient Information Forms as well as additional cases found in the MCR database to the specific geopolitical location of the study population.

"Childhood cancers are the exception to this classification..."

(Photo credit: Missouri Department of Tourism)

Methods for Detecting Space and Time Clustering

Methods for detecting space and time clustering can be either proactive or reactive. Proactive methods involve identification of potential clusters during systematic and periodic cancer surveillance activities. Reactive methods involve the detection of space and time clustering after suspicion of a cluster is reported. The rate ratios described below and the Texas method are appropriate for proactive surveillance. All methods described in this section can be used for reactive cancer surveillance.

Rates, Ratios and Confidence Intervals

Whenever possible, calculation of standardized rates and ratios will be the methods of choice to determine space and time clustering of cancer cases.

At both Level 2 and Level 3 Inquiries, whenever data are appropriate, incidence and mortality rates and the corresponding 95% confidence intervals will be calculated for the study population (as defined by study area and period of time). Direct or indirect methods for adjustment to different age distributions between comparison populations will be used.[7, 11, 12]

Rates and ratios are calculated when there are at least 30 cancer cases arising from a large enough population. For directly standardized rates, the population denominators should be at least 50,000 persons. For indirectly standardized rates, the population denominator should be at least 10,000 persons.[8, 13]

Because the standardized ratio is merely a weighted average of the age-specific relative rates (ratio of the index to the standard rate for each age group), the examination of age-specific relative rates should be implemented before any attempt is made to standardize. If the age-specific relative rates do not differ by sampling error, but instead vary systematically with age (e.g., either increase or decrease with age), no method of standardization should be applied and comparison of the index with the standard population should be made within each age group separately.

In situations when study area age-specific rates, or other variable stratum-specific rates are not available, only indirect methods can be used.

The standardized incidence and mortality ratios of the index (study) population by the comparison population (SEER or NAACCR-US or MCR-Missouri) and the 95% confidence interval are used to evaluate space and time clustering when the number of cases and denominator are sufficient to generate reliable rate and ratio estimates.

Direct Method

Using the direct method, the following steps are implemented to obtain standardized rates and ratios:

1. Define a standard population (2000 US Standard Population or the Missouri updated inter-census standard population).
2. Apply the age-specific (or other characteristic) rates of the index population (study population) to the numbers in each age group of the standard population to obtain the number of cases expected in the standard population if the index rate is applied.
3. Add the expected cases over the age groups to obtain the total number of expected cases.
4. Divide the total number of expected cases by the total in the standard population to obtain the directly standardized incidence rate (DSIR) and the directly standardized mortality rate (DSMR) for the index (study) population.

The standard population crude rate is also, by definition, a standardized rate (the crude rate standardized to the population from which the rate is estimated). The ratio of the "directly" standardized rate of the index (study) by the standard (comparison) population is the comparative rate index (comparative incidence index [CII]; comparative mortality index [CMI]). Standard errors and accompanying 95% confidence intervals in both rates and ratios will be calculated using the approximate methods.[12]

Also, the ratio of comparative indices in two communities, estimated using the same standard population (CII or CMI), equals the ratio of two direct standardized rates. In other words, direct standardized rates of two similar communities can be compared using either standardized ratios or rates (i.e., the method is consistent).

Indirect Method

Using the indirect method, the following steps are used to obtain indirectly standardized rates and ratios:

1. Define a set of age-specific (or other characteristic) rates from the comparison population (i.e., the rates obtained from SEER or NAACCR-US or MCR-Missouri in this case).
2. Apply the comparison age-specific rates to the index (study) population to get the expected number of cases in each age group.
3. Add the expected cases over the age groups to obtain the total number of expected cases.
4. Divide the total of index (observed) cases by the total of expected cases to get the standardized incidence ratio (SIR) or standardized mortality ratio (SMR).
5. Multiply the crude rate in the comparison (e.g., Missouri) population by the standardized ratio to obtain the indirectly standardized incidence and mortality rates (ISIR and ISMR, respectively) in the index (study) population.

The ratio of index cases (observed) by expected cases is the indirectly standardized SIR or SMR. Standard errors and accompanying 95% confidence intervals in both rates and ratios will be calculated using the approximate methods.[12]

It is important to mention that in the indirect method, the true standard is the index population and not the comparison populations from which rates were used to generate the expected number of cases in the index population. Therefore, the indirect standardized ratios (SIR and SMR) of similar communities, though using the same set of comparison rates, cannot be directly compared because they have different index populations; each community's own population.

Incidence or mortality ratios close to unity (i.e., close to 1) are an indication of no significant excess of cancer in the study area. Incidence and mortality ratios greater than unity for which confidence intervals do not include unity (null hypothesis) are considered an indication of cancer excess in the study population. The calculation of multiple SMRs across the sub-population inflates the type-I error when testing the null hypothesis of unity of SMR. A departure from the null hypothesis is considered when the standardized ratio confidence interval corresponds to $p < 0.025$.

Texas Method

The Texas method was designed to initiate alert and action levels of response to time clustering based on monitoring of data received by a surveillance system.[14] In proactive cancer surveillance, this method is used in conjunction with indirect methods for rate and ratio calculations (SIR and SMR) to evaluate the evidence of increases in cancer incidence or mortality over time for a study area. Because cancer cluster evaluations are usually retrospective, the Texas method is also used to evaluate sporadic aggregations of cancer in reactive surveillance (e.g., community reports of clusters).

In the Texas method, the disease experience of the study area may be monitored by an SIR (or SMR) or by Z-statistic corresponding to action and alert levels.

If the observed SIR (or SMR) or Z-statistic exceeds a pre-specified value, then an action level is reached. If the observed value falls below the action level, but above a pre-specified warning level, then an alert level is indicated. An action level is also signaled if two consecutive alert intervals are identified. The alert and action level can be expressed in terms of Z-statistic (Z_1 and Z_2) or standardized ratios (SMR_1 and SMR_2).

$$SIR_1 \text{ (or } SMR_1) = 1 + Z_1/\sqrt{(E)}$$
$$SIR_2 \text{ (or } SMR_2) = 1 + Z_2/\sqrt{(E)}$$
Where (E) is the expected value.

In order to determine the Z-statistic and the standardized ratio values, two parameters need to be specified. First is the probability that the action level will be exceeded in the first of two consecutive intervals (P_2), and second is the probability that the action threshold will be exceeded in either of the two consecutive intervals (P_3). Then, the probability of an alert will be:

$$P12 = (P_2)^2 - 2P_2 + P_3$$

After evaluation of this probability, the one-tailed Z-scores associated with P_1 and P_2 are found in the table of probability by White, Yeats, and Skipworth.[15] The Z-scores represent the critical values for the alert and action mode levels. If the number of observed cases is small (i.e., less than 30), then a Poisson distribution may be assumed, and the critical values for alert and action levels may be interpreted as standardized ratios (SIR and SMR).

Additional Methods for Detecting Space and Time Clustering

The use of additional statistical evaluation of space-time clustering is appropriate for reactive surveillance, particularly under certain circumstances:

- when at any inquiry level, the number of cases is very small (i.e., less than 10 cases for most situations) or denominator data is not available for calculating meaningful rates and ratios (i.e., population estimates by sub-population are not available or too small), or
- when at a Level 3 Inquiry, the consistency among the four space-time clustering statistical methods and the likelihood of observing the identified cluster are used to support a decision to initiate a Level 4 Inquiry.

In most situations, space-time cluster statistical methods require a case series listed over time and either a comparison population from which an expected rate can be generated (e.g., Poisson method) or a background rate for the study area (e.g., Chen method).

Poisson

In the absence of cancer cases clustering (a random occurrence) and because cancer occurrence is rare (small number of cases relative to the size of the population giving rise to cases), it is assumed that the distribution of cancer cases over time in study and comparison populations follows a Poisson distribution.[9] In this framework, the job of statistical testing is to determine if the pattern of occurrence observed is a departure from a Poisson distribution and compatible with clustering of cases over time.

The Poisson distribution has only one parameter, μ, which is both its mean and variance. The occurrence and density of cancer cases (λ) over time *(t)* follows a Poisson distribution with expected number of cases=λt=μ and var=μ.

$$P(X = x) = \mu^x e^{-\mu} / x! \qquad x = 0, 1, 2, \ldots$$

The cancer cases reported (incidence and mortality) for the index (study) population during a specified period of time will compose the "observed" cancer cases. The observed cases, depending upon the specificity of the inquiry, may be generated by gender, race and age-specific groups. This specificity is based on the knowledge about the putative exposure, cancer occurrence relationship, and mode of exposure. For childhood cancer, no further classification by gender is implemented.

The expected number of cases (μ) in the study population can be estimated by multiplying the rate in the comparison population (SEER or NAACCR-US or MCR-Missouri) during a given time period by the population at risk in the study area (Indirect Standardization). Using these facts, the Chronic Disease Public Health Epidemiologist can calculate the probability of observing "X" or more number of cases in the study population (over the time period) assuming the case occurrence follows a Poisson distribution for which the best estimate of its parameter is "x", the mean number of cases (for only one time period the mean number of cases μ equals the number of expected cases x).

$$P(X \geq x) = \sum_{x=x}^{x=\infty} \mu^x e^{-\mu} / x! \qquad x = 0, 1, 2, \ldots$$

Conversely, one can calculate

$$1 - [P(X < x) = 1 - \sum_{x=0}^{x=x-1} \mu x e - \mu^x e^{-\mu} / x!] \qquad x = 1, 2, 3, \ldots$$

In other words, what is the probability of observing "x" or more number of cases in the study population when the expected number of cases in the state is μ? It is assumed that when this probability is smaller than α=0.001, there is an excessive number of observed cases.

Chen

The Chen method is designed to detect only temporal aggregates of disease.[9]
It compares the length of the observed time interval between successive cases with a critical interval based on the background rate of disease and the size of the population at risk. If each of the observed time intervals is shorter than the critical interval, a significant increase is determined.

For this method, a series of cases observed over many time periods is listed by date of occurrence. If sufficient data is available, this list may be further classified into gender, race and age-specific groups. The observed length of time elapsing between the occurrences of consecutive cases is the variable of interest.

The Expected Time Interval (ETI) between successive cases in the study population during the study period is:

$$ETI = 12 * (1 / \text{expected number of cases per study period})$$

In order to determine the number of cases per study period, one must first know the prior background rate (incidence or mortality) of the cancer of concern in the study area. Then, multiply this rate by the population of the community estimated in the middle of the study period.

The critical interval is found by multiplying the ETI between cases by a constant K.
K is defined as:

$$K = -\log(1 - p_0(n)^{1/n})$$

Where log is the natural logarithm to the base e
$p_0(n)$ is the probability of type-I error (e.g., 0.05)
n is the number of intervals between the first and the last case within the total period of the study.

Significant Value: A significant value is when each of the n observed intervals is shorter than the critical interval estimated (i.e., $ETI * K$).

Knox

The Knox method is useful to detect clustering occurring in both space and time.[9] All combinations of two cases and each of the two possible pairs are identified according to their spatial and temporal proximity to one another. Each case is identified in the X-Y coordinate plane. The critical time and space intervals are used to determine the temporal and spatial proximity. The latency of the disease of interest and the population at risk will determine the critical intervals. Therefore, a total of N (N-1)/2

pairs, clustered in space and time, can be represented in a two-by-two table: Cell A denoting case-pairs that are close in space and time, cell B denoting case-pairs close in space, cell C representing case-pairs close in time, and cell D indicating case-pairs neither close in time nor space. The column totals are M1 and M2, denoting totals for pairs close in time and not close in time, respectively. Row totals N1 and N2 indicate totals for pairs close and not close in space, respectively. If one continues to adjust these two measures of closeness until N1/N and M1/N are nearly equal to a prescribed fraction (e.g., 0.10), then the expected value of A is (0.1) (0.1) N = 0.01N. It follows:

Expected Value of A (m) = (N1)(M1)/N

A = x is the observed value of A

Then the probability of observing at least x cases given the expected number (m) is:

$$P(X \geq x) = \sum_{x=x}^{x=\infty} m^x e^{-m} / x! \qquad x = 0,1,2,\ldots$$

OR

$$1 - P(X < x) = \sum_{X=0}^{X=x-1} m^x e^{-m} / x! \qquad x = 1,2,3$$

	TIME			
		+	-	Total
SPACE	+	A	B	N1
	-	C	D	N2
	Total	M1	M2	N

Barton

The Barton method is adequate to detect changes in spatial pattern over time.[9] It utilizes an approach similar to analysis of variance.

If (f) is the period in which all cases occur and (n) is the total number of cases in this period, then the average interval length (d) between successive cases is:

d = f / (n+1), for cases observed over the time period.

When the first case and the last case mark the beginning and the end of the period, then the average interval is:

d = f / (n-1).

If the time interval between cases in a series is less than the average interval (d), then temporal clustering is present. There are (h) clusters of cases aggregated in a time interval and each time interval is a "time cell". The x-y coordinate plane is used to define a coordinate for each case using a grid. In this situation, an interaction between time and space is defined when cases close in space also tend to be close in time. If there is no interaction between space and time, then one expects that the average squared distance between the "centroids" of cases within each temporal cell and the overall centroid would be similar to the average squared distance between all cases in the sample (D) and the overall centroid. The statistics of interest are:

Where Q = ratio of squared distances among (h) temporal cells to the mean squared distance between all cases (D);

$V(Q)$ = Variance of Q and $\sqrt{V(Q)} = Sd(Q)$

A transformation of Q follows the F distribution

When the number of h temporal clusters are >3*Sd (Q) * N cases +1

Then Q follows a normal distribution

Then $Z = (Q - 1) / Sd(Q)$

Pearson

The Pearson method is used to detect spatial clustering.[9] It determines the probability that a distribution of cases within spatial cells is consistent with the null expectation that cases are randomly distributed among cells of equal size determined by population count.

Cells of same population size are defined by a geographical grid superimposed over a study area or by other convenient parameters such as a census tract, census block or household.

It follows that with (n) cases and (m) cells, the number of cases per cell of interest is denoted by (s) and the observed number of cells with (s) cases is denoted by $(P)_s$.

Therefore the expected value $(\overline{P}_s) = m\binom{n}{s} p^s q^{(n-s)} \qquad s = 0,1,2,\ldots,n$

Where $p = 1/m$ and $q = 1 - p$

The probability of observing a particular distribution of (n) cases among (m) cells is then estimated from the likelihood chi-square test.

$$X^2 = \sum_s r_s^2$$

Where $r_s^2 = 2P_s\left[\log\left(\frac{P_s}{\overline{P}_s}\right) + \left(\frac{\overline{P}_s}{P_s}\right) - 1\right] \qquad DF = K - 1$

Where (K) is the number of different cell occupancy configurations observed

Grimson

The Grimson method evaluates the evidence of clustering among adjacent areas (e.g., counties, ZIP, etc.).[15] It determines whether high-risk areas cluster spatially within a larger area. It compares the observed number of adjacent borders shared among high-risk areas with an expected number. The expected number of adjacent borders assumes that high-risk areas are randomly distributed within the study region.

Given a maximum of N (N-1) / 2 pairs of areas, the probability of K adjacent counties follows a Poisson distribution.

$$P(X = x) = \mu^x e^{-\mu} / x! \qquad x = 0,1,2$$

Then the important statistics are Mean of (K) and Var of (K)

Mean of (K) = Expected value (K)= μn (n-1) / 2 (N-1)

If n is small and N is large

Then K follows a Poisson distribution and E(K) = V(K) = μ

If n / N is large, the probability of K follows a normal distribution

Ohno

The Ohno method is designed to detect geographical aggregation of cases.[9] If adjacent areas experience levels of disease which are "more alike" than would be expected by chance, then clustering is present.

If a study area is partitioned into meaningful geographical boundaries, there are N cells and a total of "A" adjacent cell pairs. Also, if the rate of disease in each cell is calculated and rates are categorized into two or more levels, there are n_i cells in each rate category.

For N cells, there are a total of N (N-1) / 2 possible disease category pairs, n_i (n_i-1) / 2 possible like-pairs within a category subset. Therefore, the total number of adjacent pairs observed is compared to the expected number of adjacent pairs.

$$[A/N(N-1)][n_i(n_i-1)/2]$$

And, to the expected number of like pairs

$$[A/N(N-1)][\sum n_i(n_i-1)/2]$$

The variable observed minus expected will follow a chi-square distribution with one degree of freedom.

REMSA

The REMSA method uses person, place, and time dimensions to determine whether particular occurrences tend to be non-randomly distributed within certain subgroups defined by demographics and/or geographical location and/or time.[9] This method is useful when disease etiology is unknown and one needs to explore leads about disease risk factors.

The underlying study population is partitioned into study attributes (e.g., sex, race, place, month / year of diagnosis or death) and the proportion of the population that falls in each category is determined. Assuming independence among category-specific proportions, one can indirectly estimate the proportion of the population that falls in a sub-category determined jointly by two or more attributes by multiplying category-specific proportions. Population-based sample surveys can also be used to directly estimate these sub-category specific proportions.

Given N total cases distributed among all of the cells, and the probability of selecting a given cell equal to p, the probability of observing at least x of the N cases in that cell follows a binomial distribution:

$$P(X \geq x) = \sum_{x=x}^{x=n} \binom{n}{x} p^x (1-p)^{(n-x)} \qquad x = 0,1,2,\ldots$$

Notes:

(Photo credit: Missouri Department of Tourism)

Limitations of Methods

General

Observations brought to the attention of public health officials are by definition "unusual" and therefore a "non-a priori situation." In this instance, statistical significance has little meaning.

Another issue is the many (more than expected) occurrences of cancer clusters, observed when cancer cases are distributed in an ever-increasing number of arbitrarily defined study areas. In the words of Bender "if an area is examined in detail for a long period of time, a statistically significant excess of cancer cases will be observed."[16] Clusters are not rare occurrences. With 291 million people in the United States (2003 population estimate, USA QuickFacts, U.S. Census Bureau) and many types of cancer, chance alone may explain many identified clusters. Clusters occur continually within any large population, and their population occurrence is often no greater than that expected by chance alone. Therefore, cancer clusters often represent "expectedly unexpected events."[17]

Also, at both Level 2 and Level 3 of the CI Inquiry process, many statistical tests may be implemented in the same population, constituting what is called a multiplicity of statistical testing. When multiplicity is present, the likelihood of making a type-I error is much greater than that occurring by chance alone. In order to minimize this problem, the recommendation is to use a stricter level of acceptance for making a type-I error.[17]

In addition, the manner by which cancers are detected can affect rate comparisons. Screening and early diagnosis may change over time and by region. The rate comparisons and the statistical testing utilized assume this bias is not operating. Therefore, these variations may result in spurious differences when comparing rates and counts by time periods and regions.[18]

Both screening and diagnostic technique changes that are differential across regions and time periods can affect cancer staging. Distant stage (metastatic) cancer at some point in time may have been misclassified as localized or regionalized cancer at an earlier date due to this bias.[19]

Rate Standardization and Texas Method

In the case of a small-size index population, direct method estimates are unreliable. The variance of both directly standardized rates and ratios tends to be large compared to that estimated using the indirect method. This unreliability of the direct method may affect decisions regarding evidence for clustering based on the size of the ratios and the 95% confidence interval.

When rates are calculated using the direct method, rate differences and ratios, confidence intervals and statistical testing are inaccurate if fewer than 10 cases are used to generate rates. No rate comparisons should be attempted if fewer than 6 cases are available.[19]

The application of the Texas method requires knowledge of the distribution of the index (study) population. For small communities, this information is not always readily available. Both the indirect method for standardization and the Texas method suffer from lack of consistency when making comparisons among communities.

Also, because indirect standardized ratios (SIRs and SMRs) are based on the age (or other factor) distribution of the index (study) population (rather than the standard population), they are prone to change if there is a shift in the age (or other factor) distribution of this population over time. Therefore, comparison of SIRs or SMRs over time may, in effect, represent "different populations" as a result of demographic shifts.

> "(Cancer) *Clusters are not rare occurrences*"

Poisson and Chen Methods

The application of the Chen method requires knowledge of the population distribution and the baseline rate of the cancer of concern in the study area. Many cancer inquiries originate from small communities, for which expected rates are difficult to determine. The rates in these small communities are often unreliable, leading to substantial error in estimating expected rates and therefore ETIs.

Another limitation of the Chen method and also of the Poisson method is that these measures are not conventional parametric statistics. Therefore, a more conservative approach is recommended to prevent an increase in type-I error. The recommended p-value for decision criteria is $p \leq 0.001$.[14]

Knox and Barton Methods

The main limitation of the Knox method is the dependency of results on the critical space-time distances (intervals) specified. This dependency may lead to considerable data "fishing" by re-testing after changing of space-time critical distances. Both methods may also lose power by using the actual distance between case-pairs in the geographic coordinates. However, the use of geographical coordinates for each case in a continuous fashion allows the Barton method to overcome the subjectivity of determining spatial proximity present in the Knox method.

A limitation of both the Knox and Barton methods is the reliance on the criterion for determining statistical significance on space-time interaction. If clustering is present in one dimension alone, either space or time, the test statistics are likely not significant. However, a major strength of both methods is that they do not require prior knowledge of the size of the underlying population, values of demographics and baseline frequencies of disease occurrence or rates.

Pearson Method

A major weakness of the Pearson method is the assumption that the population at risk is the same in each of the probability cells. In most situations, this assumption does not hold. Also, because the cells are frequently arbitrarily defined, observation of clustering within a set of cells may have little practical significance. This can be overcome, however, by exploring different cell configurations (e.g., CT, block, etc.).

Grimson and Ohno Methods

A major limitation of both the Grimson and the Ohno methods is that counties (ZIP or CTs) sharing a few miles of border are considered equivalent to counties sharing dozens of miles. In addition, in both methods, counties that have many borders have a greater likelihood of random clustering compared to those with only one or two borders. Nonetheless, the Grimson method's strength is the tailor-made probability distribution because it eliminates concern regarding appropriateness of alternative distributions. Although the Ohno method uses an alternative distribution, the chi-square, its validity has been demonstrated through Monte Carlo simulation.

REMSA Method

This method relies on the multiplication of probabilities for independent events. If attributes of the study population being evaluated are not independent, the occurrence of events will not be independent. This situation is likely to occur when evaluating clustering by person, place, and time. For example, if the study population is 50% African American and 80% high socio-economic status (SES), the REMSA method assumes the population of African Americans who are high SES to be 40%. It is possible, however, that the high SES and African-American population composes only 10-20% of the study population.

(Photo credit: Missouri Department of Tourism)

Epidemiological Translation

As mentioned in the section titled "Epidemiological Evaluation of Clustering," application of epidemiological criteria for disease causation and reasoning should guide the CI process. Statistical tools are used to assist in making a decision about the existence of a cluster, never to determine this decision.[7]

The criteria for causality of an association that guides the epidemiologist, and therefore the CI process, are the consistency, biologic plausibility, and evidence of dose-response.

The consistency criterion requires a wide knowledge base of the natural history and descriptive epidemiology of the reported cancer(s) as well as the use of a systematic literature review that incorporates the principles of evidence-based research. In terms of cluster investigation, consistency may mean any of the following:[9]

- Historical patterns in the reported cases;
- Pattern(s) of occurrence consistent across reported literature;
- Homogeneity of reported cases (e.g., same sex, race, age or occupation; same cell type, anatomic site or pathway of exposure); and/or
- Consistency within aggregation (within cluster).

Biologic plausibility requires a strong knowledge of the disease process of concern and reliable information on environmental exposure of interest. In the context of a CI, the biologic plausibility may mean any of the following:

- Presence of an environmental or occupational risk (e.g., asbestos abatement and mesothelioma);
- Demonstration that a pathway for exposure is possible; and/or
- Recognition that a specific organ or tissue is a possible site for biologic action of the suspected exposure.

In analytical epidemiology and medical research, dose-response is considered by far one of the strongest criteria for determining a causal association. However, cluster investigations are hypothesis-generating types of research, as opposed to analytical studies that are designed to test hypotheses of causation. This difference is carried over to the careful application of criteria and the interpretation of the findings of a cluster investigation. Often the dose-response is evaluated against the time continuum. For this reason, a series of reported cases over a long period of time is usually required to assess this criterion in a meaningful way. Sometimes dispersion of spatial patterns may also be used to assess dose-response.

In a cluster investigation, dose-response usually means:

- Duration of exposure (e.g., a greater proportion of cases with long-term residency in the proximity of the hazard or proximity in time of suspected events).

In a cluster investigation, dose-response less often means:

- Identification of a specific spatial pattern of dispersion (e.g., the closer the proximity to the exposure, the greater the number of observed cases); or,
- A combination of duration of exposure and spatial pattern of dispersion.

Appendix A

Report Outline

Inquiry No:

Location:

Received:

Initiator:

Type(s) of Cancer Reported:

Suspected Cause(s):

Summary of Inquiry:

Data:

Patient Information:

Criteria (Changes with each level of progression.):

1. A definable type of cancer is reported.
2. Only one type of cancer is reported or the types of cancer reported must have common suspected risk factors (based upon the existing database of risk factor literature searches) including exposures that have been reported to be a possible cause of multiple tumors (e.g., dioxin and radiation).
3. There is a specific environmental or occupational cause (exposure) suggested for this excess.
4. There must be a plausible scenario for the patients to have come into contact with the suspected cause of their cancer.
5. There is no evidence of common behavioral-type or other risk factors with strong, well-proven relationships to cancer such as those between smoking and lung cancer; between polyvinyl exposure in occupational setting and angiosarcoma; and between asbestos and mesothelioma.

In addition to the five above criteria, the inquiry must meet at least two of the following criteria to move to Level _____. (Changes with each level of progression.)

1. A common type of cancer is occurring in an unexpected age group.
2. A rare type of cancer is reported.
3. Based on available knowledge base and research, the suspected exposure is plausibly linked to the cancer(s) of concern.
4. If the cancer latency in relation to a particular exposure is known, there must be a reasonable match between the estimated time cases have been exposed and this latency. Unless the cluster is in an occupational setting, the time a case has been exposed is estimated by the time a case lived in the area of concern and the time exposure was first established. If the cluster is in an occupational setting, the time a case has been exposed is estimated by the time a case was employed in the setting of concern and the time the exposure was first established. For most cancer sites, if cancer latency is not known a minimum of ten years residency in the study area or exposure in the occupational setting is necessary for the suspected association to be considered plausible. Childhood cancer may have a shorter latency period.

Recommendations:

APPENDIX B

Sample Initial Response Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Date CI00-000

Name
Address
City, State, ZIP

Dear <name>:

Thank you for your <phone call/e-mail> concerning possible excess of <specific if appropriate> cancer cases linked to <suspected cause>. As discussed in our <telephone conversation/ e-mail>, the <preliminary report/available data> show <higher/lower/similar> incidence and mortality rates of <type> cancer in <name> County as compared to the state. <Include BRFSS or screening statements if appropriate, such as: Smoking rates are also higher in the area as compared to the state.> A cancer inquiry will be initiated as requested during our conversation.

You are at the first step in the cancer inquiry process. Please distribute the enclosed Cancer Patient Information Forms to those individuals with cancer in your community of concern. Explain to them why you have initiated this cancer inquiry and that this information is necessary to assist the Missouri Department of Health and Senior Services (DHSS) in investigating your concern. Information in this letter can assist you in this process. Due to confidentiality requirements, each individual needs to return his or her own form to the Missouri Department of Health and Senior Services, Bureau of Cancer and Chronic Disease Control, Cancer Inquiry Program, P.O. Box 570, Jefferson City, MO 65102-0570. (The address is printed on the form.) **It is important that these forms be returned**, so ask each person to provide as much information as possible.

Please ask each individual to return the enclosed forms within 6 weeks. It is important that you follow-up with them to find out if the forms have been returned. If we do not receive any forms within six weeks, our office will assume that no further action is necessary and will close the inquiry. If more than six weeks is needed to complete and mail the forms, please call 573-522-2840.

As you are working on this concern, realize that although cancer is very serious and frightening, it is a surprisingly common disease. Current information shows that approximately one out of three Americans will develop cancer in their lifetime, and cancer will affect three out of four families. Also, the risk of developing cancer increases with age, so as the population ages, more cases of cancer in our communities are expected.

It is important to realize that cancer is not one disease, but many. It can occur in almost any part of the body. Each cancer type develops differently and has different risk factors. For example, the main risk factor for lung cancer is cigarette smoking, but for skin cancer it is sun exposure. On the other hand, it really isn't known what causes some cancers like breast cancer.

Many people believe that something in the environment causes the cancer they see in their community, but behavior accounts for most of the known cancer risk. Such factors as smoking, poor diet, heavy alcohol use, and sexual and reproductive history can all contribute to developing cancer. It is estimated that less than 10% of cancers are caused by environmental exposures. In contrast, cigarette smoking alone causes about 30% of cancer. In addition, family history is important and contributes to some types of cancer.

Most cancers take a long time to develop, some as many as 40 years. It is usually decades from the time someone is exposed to something that might cause cancer to the time that cancer is discovered. This is one of the reasons that cancer is more common in older adults. In addition, the few chemicals that are linked to cancer must have fairly long and concentrated exposures before they will actually cause cancer.

An apparent increase of cancer in one community or group is called a cancer cluster. If a cluster includes cancers of different types, it is probably not a "true" cancer cluster. For example, if someone called and reported that there were many people with cancer in their community, but the kinds of cancer included lung, breast, leukemia, and prostate, it is usually determined not to be a "true" cancer cluster. Most of our knowledge about cancer causes comes from studies comparing many people with the same cancer to people who do not have cancer. Investigation of a few people with different cancers will not shed light on the cause of cancer because different things probably caused those cancers. That is why, in order for the DHSS Cancer Inquiry Program to conduct an inquiry, it is important to know the details about the type(s) of cancers that seem to be part of a cluster. DHSS does have a procedure to examine potential cancer clusters. A "true" cancer cluster usually has one or more of the following characteristics:

- only one type of cancer is involved;
- the cancer is occurring in an unexpected age group;
- there is a very rare type of cancer involved;
- there is a scientifically established causal relationship between the type of cancer and the suspected exposure.

The fact that cancer is common does not mean that you, your family, or DHSS should not be concerned. Many cancers are preventable, and early detection saves lives as well as associated medical costs. There are national and state goals to lower the number of people with cancer. In order to accomplish this, awareness about cancer prevention and screening needs to increase. Thank you for your interest in this issue.

Enclosed are several items to help you understand more about cancer: *What is Cancer?* by the Agency for Toxic Substances and Disease Registry; and *The Burden of Cancer in Missouri* produced by DHSS. Additional information can also be obtained at these Web sites:

- http://www.dhss.mo.gov/CancerinMissouri
- http://www.dhss.mo.gov/CancerInquiry

The DHSS Web site can also provide valuable cancer data using the Missouri Information for Community Assessment (MICA). The public, as well as researchers, local public health agencies, and others can access cancer data on MICA at www.dhss.mo.gov/MICA/.

This letter is being copied to several other health agencies and officials to inform them of the cancer concern in the community. To assure confidentiality, your name and address will not be included on those copies. If you have questions, please call 573 522-2840.

Sincerely,

<name>
Cancer Inquiry Coordinator

<initials>:<initials>

Enclosures

c: <name>, Chief, Bureau of Cancer and Chronic Disease Control
<name>, Administrator, Section for Chronic Disease Prevention and Nutrition Services
<name>, Director, Center for Local Public Health Services
<name>, Chief, Bureau of Environmental Epidemiology
<name>, Administrator, Section for Disease Control and Environmental Epidemiology
<name>, Public Health Epidemiologist, Office of Epidemiology
<name>, Chief, Office of Public Information
<name>, Administrator, <name> Local Public Health Agency

Appendix C

Cancer Inquiry Initial Report Form

Initial Date:	(mm/dd/yyyy):	Please check the appropriate category ☐ CC ☐ CI No. _____ — _____
DHSS Employee Completing Form:		
Inquirer Information		
Name		
Title of Group Represented (if applicable)		
Address		
City/State/ZIP		
Best Time to Contact (Day, Evening, Weekend, specific time, etc.)		
Telephone Number(s) (Numbers to contact you.)		(☐☐☐) ☐☐☐ - ☐☐☐☐ (☐☐☐) ☐☐☐ - ☐☐☐☐
E-Mail Address(es)		
Concern Information		
City/Town Name		
County Name		
ZIP Code(s) (Zip codes of area of concern)		
Geographical Boundaries (Provide street names, if possible, of the area of concern; draw a map if needed.)		
Suspected Environmental Cause(s) (Describe what you suspect is causing the cancer in the community.)		
Exposure (Provide information on how people were exposed, i.e., air, water, on the job, etc.)		
Level of Interest		
No. of Patient Information Forms Requested ☐☐		No. of Patient Information Forms Expected to Return ☐☐
Type(s) of Cancer of Concern (e.g., breast, colon, brain)		
Time period of Diagnoses (e.g. 1989-1994) ☐☐☐☐ to ☐☐☐☐	Time period of Exposure (e.g. 1965-2001) ☐☐☐☐ to ☐☐☐☐	Is exposure still occurring? ☐ Yes ☐ No
Have you spoken to any other government agency about this possible exposure? ☐ Yes ☐ No		
Public Officials Contacted		
Name		
Title		
Agency		

Initial Date:	(mm/dd/yyyy):	Please check the appropriate category. ☐ CC ☐ CI No. _____ — _____
DHSS Employee Completing Form:		
Address		
City/State/ZIP		
Telephone Number(s)		
E-Mail Address(es)		
Name		
Title		
Agency		
Address		
City/State/ZIP		
Telephone Number(s)		
E-Mail Address(es)		
Name		
Title		
Agency		
Address		
City/State/ZIP		
Telephone Number(s)		
E-Mail Address(es)		

Summary of Conversation (Date | Notes)	

Appendix D

Cancer Patient Information Form

Patient Information Form

MISSOURI DEPARTMENT OF HEALTH AND SENIOR SERVICES

PATIENT INFORMATION FORM

Inquiry # or name
(e.g. CI 08-005, Cameron)

_____

This form is being given to you as the first step in exploring a concern regarding cancer or benign tumors of the brain and central nervous system (CNS) in your community. The person that gave it to you will explain the nature of the concern. The fact that you were given this form does not mean that there is a known problem in your community. It simply means that the person who gave it to you would like the Missouri Department of Health and Senior Services (DHSS) to look at information from those with cancer or benign brain and CNS tumors in the community to determine if there may be a problem. Your information will be kept confidential, and **will not** be shared with the person who gave you the form. For questions about the process please call (573) 522-2841.

Please print and fill in all of the information as completely as possible for you, if you are the individual with cancer or a benign brain or CNS tumor, or for your family member who had cancer or a benign brain or CNS tumor but is no longer living. At a minimum you should include legal name, birth date, social security number, how long you lived in the area (community of concern), and where you were diagnosed with cancer (name of hospital, physician or clinic). This information allows the DHSS to confirm the information and use it to look into the concern. If additional space is needed, use the back of the form or attach a separate sheet of paper.

Legal Name (Last Name, First Name, Middle Initial)	
☐ Male ☐ Female	Social Security Number ☐☐☐-☐☐-☐☐☐☐
Current Address (Street / City / State / Zip)	
Phone Number (☐☐☐)☐☐☐-☐☐☐☐	County
Birth Date (mm/dd/yyyy) ☐☐/☐☐/☐☐☐☐	Death Date (mm/dd/yyyy) ☐☐/☐☐/☐☐☐☐
Type of Cancer:	Date of Diagnosis (mm/dd/yyyy) ☐☐/☐☐/☐☐☐☐
Address at Time of Diagnosis (street, city, state, zip and **county**)	
Physician's Name	Facility name where you (or your family member) were first diagnosed with cancer. (Hospital or other facility)
Address when environmental exposure may have occurred (include street, city, state, zip and **county**) (For example, the address where you or your family member lived as a teen.)	
Number of years you or your family member lived at the address where exposure may have occurred.	☐☐
Do you currently smoke? ☐ Yes ☐ No	If you don't smoke now, what year did you quit smoking? ☐☐☐☐
Did you ever smoke? ☐ Yes ☐ No	How long did you smoke? ☐☐ Years
Additional Information & Comments: (Please feel free to provide additional information in this section or on the back. For example, maiden names, previous names used, if any. Information about you or your family member's occupation, exposure, etc.)	

Person Completing Form (if other than patient): _____

Relationship to patient: _____

Phone Number: _____ Is patient aware of this form? __Yes __No

Please return within 6 weeks of receipt to:

Bureau of Cancer and Chronic Disease and Control, Cancer Inquire Program
Missouri Department of Health & Senior Services
P.O. Box 570, Jefferson City MO 65102-0570

OR via fax (573) 522-2899
OR (573) 522-2898

Appendix E

Sample Initial No Response Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

DATE CI00-000

XX XXXXX XXXXXX
XXXXX X XXXX XXXXX
XXXXX XXXXXX XX XXXXX

Dear XX XXXXXX:

A letter and Cancer Patient Information Forms were sent on <date> requesting your assistance in researching your concerns about an excess of cancer cases in your community. Upon review, our files indicate that no forms have been received and we have not been contacted for a time extension. These forms are necessary to proceed with the inquiry.

Because no further research into your concerns can be done without the Cancer Patient Information Forms, the CI Program will consider this inquiry closed if our office does not receive a response within two weeks of the date of this letter. If additional time is needed for individuals to send us the Cancer Patient Information Forms, simply notify this office and we can provide up to an additional four weeks.

As with our previous letter, your name and address have been omitted from the copies being sent to other offices to maintain your confidentiality. The copies serve to inform those offices of the status of the cancer concern in the community.

Additional cancer information can be obtained at these Web sites:

- http://www.dhss.mo.gov/CancerinMissouri
- http://www.dhss.mo.gov/CancerInquiry

If you have any questions, please call 573-522-2840.

Sincerely,

<name>
Cancer Inquiry Coordinator

<initials>:<initials>

c: <name>, Chief, Bureau of Cancer and Chronic Disease Control
<name>, Administrator, Section for Chronic Disease Prevention and Nutrition Services
<name>, Director, Center for Local Public Health Services
<name>, Chief, Bureau of Environmental Epidemiology
<name>, Administrator, Section for Disease Control and Environmental Epidemiology
<name>, Public Health Epidemiologist, Office of Epidemiology
<name>, Chief, Office of Public Information
<name>, Administrator, <name> Local Public Health Agency

Appendix F

Final No Response Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

DATE CI00-000

XX XXXXX XXXXXX
XXXXX X XXXX XXXXX
XXXXX XXXXXX XX XXXXX

Dear XX XXXXXX:

A letter and Cancer Patient Information Forms were sent on <date>, and a follow-up letter was sent on <date>, requesting your assistance in researching your concerns about an excess of cancer cases in your community. Upon review, our files indicate that no forms have been received, nor have we been contacted for a time extension.

Because no further research into your concern can be completed without this information, the inquiry is now closed. Your name and address have been omitted from the copies of this letter being provided to other offices to maintain your confidentiality. The copies serve to inform those offices of the nature of, and status of, the cancer concern in the community. Additional cancer information can be obtained at these Web sites:

- http://www.dhss.mo.gov/CancerinMissouri
- http://www.dhss.mo.gov/CancerInquiry

If you have any questions, please call 573-522-2840.

Sincerely,

<name>
Cancer Inquiry Coordinator

<initials>:<initials>

c: <name>, Chief, Bureau of Cancer and Chronic Disease Control
<name>, Administrator, Section for Chronic Disease Prevention and Nutrition Services
<name>, Director, Center for Local Public Health Services
<name>, Chief, Bureau of Environmental Epidemiology
<name>, Administrator, Section for Disease Control and Environmental Epidemiology
<name>, Public Health Epidemiologist, Office of Epidemiology
<name>, Chief, Office of Public Information
<name>, Administrator, <name> Local Public Health Agency

Appendix G

Sample Confirmation Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED CI00-000

DATE

NAME
ADDRESS
CITY, STATE, ZIP

Dear <name>:

This letter is to confirm that the Missouri Department of Health and Senior Services Cancer Inquiry Program has received Cancer Patient Information Forms. Thank you for facilitating the return of these forms.

The next step in the Cancer Inquiry process is to verify the information on the Cancer Patient Information Forms with Missouri Cancer Registry records. The information is then compared against a set of criteria to determine if further research is required. This may take between a few weeks to a few months to complete. Your patience during this time is appreciated. The Cancer Inquiry staff will communicate the results to you as soon as possible.

This inquiry will be discussed at the next Cancer Inquiry committee meeting scheduled for <date>. If it is determined that there is no clustering of cancer cases in your community and the identified environmental exposure does not represent a community health hazard, a letter describing the findings will be forwarded within <number> weeks after the Cancer Inquiry committee meeting. However, if it is determined that there is a possible cancer cluster, further research and evaluation may take an additional two to three months to complete. After this evaluation is complete, the Cancer Inquiry staff will provide a detailed description of the findings.

Please feel free to contact the Cancer Inquiry staff at (573) 522-2840 to provide any new information that may be helpful or to ask questions.

Sincerely,

<name>
Cancer Inquiry Coordinator

<initials>:<initials>

c: <name>, Chief, Bureau of Cancer and Chronic Disease Control
<name>, Administrator, Section for Chronic Disease Prevention and Nutrition Services
<name>, Director, Center for Local Public Health Services
<name>, Chief, Bureau of Environmental Epidemiology
<name>, Administrator, Section for Disease Control and Environmental Epidemiology
<name>, Public Health Epidemiologist, Office of Epidemiology
<name>, Chief, Office of Public Information
<name>, Administrator, <name> Local Public Health Agency

Definitions

Age-Adjusted Rate ..... A procedure for adjusting rates, designed to minimize the distortions created by differences in age distributions (and permit fair comparisons) when comparing rates for populations with different age compositions. This calculation is useful when comparing rates from different populations or in the same population over time. Age-adjusted rates are calculated by weighting the age-specific rates for a given year by the age distribution of a standard population. Source: Commonwealth of Massachusetts Department of Public Health. *Heart disease and cancer*. Retrieved February 16, 2006, from http://ww.mass.gov/dph/bhsre/death/96/dth96app.htm).

Summary rates based on the actual number of events (e.g., birth, deaths, or diseases) in a total population over a given time period. Source: Mausner J.S., and Kramer, S. (1985). Mausner and Bahn Epidemiology: An introductory text. Philadelphia, PA: W.B. Saunders Company.

Age-adjusted rates are rates that would have existed if the population under study had been distributed by age the same way as in a "standard" population. Age-adjusting is a way to make fairer comparisons between populations with different age distributions, by eliminating differences in observed rates that result from age differences in population composition. For example, a county having a higher percentage of elderly people may have a higher rate of death or hospitalization than a county with a younger population, merely because the elderly are more likely to die or be hospitalized. The same distortion can happen when we compare races, genders, or time periods. Age-adjustment makes the different groups' rates more comparable. Age-adjustment in this document is done by the direct method: applying age-specific rates in the population of interest to a standard age distribution. The standard for age-adjusting death rates is the projected year 2000 U.S. resident population. [See "Age-specific rates" and "Standard population."] Each age-specific rate is multiplied by the proportion of the standard population that was in that age group. Then the age-specific results are added up to get the age-adjusted death rate for the area of study. Sources: Adapted from "NCHS Definitions" at http://www.cdc.gov/nchs/datawh/nchsdefs/ageadjustment.htm#aarates and from the Missouri DHSS Web site data documentation at http://www.dhss.mo.gov/CDP_MICA/AARate.html.

Age Specific Rate ..... Rates computed by dividing the number of events (e.g., deaths) in an age group in an area by the estimated population of the same age group/area and then multiplying by 100,000 or the appropriate multiplier. Age-specific rates are used in computing age-adjusted rates. Based on: Anderson RN, Rosenberg HM. Age Standardization of Death Rates: Implementation of the Year 2000 Standard. Source: National vital statistics reports; vol 47 no. 3. Hyattsville, Maryland: National Center for Health Statistics. 1998, found at: http://www.cdc.gov/nchs/data/nvsr/nvsr47/nvs47_03.pdf.

Biological Plausibility ..... A causal association (or relationship between two factors) is consistent with existing medical knowledge. Substances may produce illness in a variety of ways such as direct invasion, through the production of a toxin, allergic reaction, etc. This term refers to whether it is likely that a given substance caused the specific disease in a manner that is believable or possible.

Case Analytical Study ..... The testing of hypotheses (i.e., testable assumptions) to determine if the differences between two or more variables are independently occurring.

Case Ascertainment ..... The process of identifying new cases through an active search of existing cancer databases.

Case Verification ..... The process of verifying the accuracy of information on each case submitted. The MCR database is the usual data source for case verification.

Cancer Incidence ..... Incidence rates express the number of new cases diagnosed in a population with respect to the size of the population and the time period under study. Source: Havener L (Ed). Standards for Cancer Registries Volume III: Standards for Completeness, Quality, Analysis, and Management of Data. Springfield (IL): North American Association of Central Cancer Registries. October 2004.

The frequency (number) of new occurrences (cases) of cancer reported in a specified period of time (e.g., a year) divided by the number of persons in the population (e.g., county, region, state, etc.) during the time period being studied. Source: Brownson, R.C., Remington, P.L., and Davis, J.R. (1998). *Chronic disease epidemiology and control* (2nd ed.). Washington, DC: American Public Health Association.

Cancer Cluster ..... A greater-than-expected number of cancer cases that occurs within a group of people in a defined geographic area over a specific period of time.

Confidence Interval (CI) ..... Range of values for a rate that will include the true value of the rate a given percentage of the time. Example: 95% CI includes the true value of the rate 95% of the time.

Crude Rate ..... A rate is a measure of some event, disease, or condition in relation to a unit of population, along with some specification of time. For example, a crude death rate is calculated by dividing the number of deaths in a population in a year by the number of persons in that population. The term "crude" distinguishes rates calculated as just described from rates that are adjusted for some characteristic, such as age. [See Age-adjusted rate.] Death rates are expressed as the number of deaths per 100,000 population; rates for other events or conditions may use other multipliers. (DHSS and NCHS use un-rounded census counts of the resident population, as of April 1, for census years. For other years, the estimated midyear resident population is used.) Source: Adapted from "NCHS Definitions" at http://www.cdc.gov/nchs/datawh/nchsdefs/rates.htm#crudedeath.

Death (Mortality) Rate ..... The number of deaths in a given population during a given time frame in a given geographic area generally expressed per 100,000 population.

Environmental Assessment ..... Evaluation of the environment to identify an agent, or agents, that may cause cancer.

Epidemiology ..... The study of the patterns, causes, and control of diseases in human populations.

Etiological Study ..... A study that attempts to determine the cause or causes of a specific disease or condition.

Feasibility Study ..... A determination as to whether all the needed elements (e.g., data, time, manpower, etc.) are available for completing an analytical study.

Latency or Latent Period ..... The length of time between when a person is exposed to an environmental agent and the onset of the disease. May also refer to the period of time between the onset of risk factors and diseases they cause.

Plausible ..... Likely, believable or credible.

Population ..... The number of residents of a given geographic area.

Population Estimates ..... The figures attempt to gauge the number of persons (by age and sex and, for select counties, race) living in Missouri and its 115 counties. Population estimates are produced and developed by analysts at DHSS using, in large part, inputs from the US Census Bureau and the Federal State Cooperative Program for Population Estimates. **Or,** an estimate of the total population and population age groups for Missouri and its counties, prepared by the US Census Bureau and Missouri Office of Administration under the Federal-State Cooperative Program for Population Estimates. Source: DHSS. *Population estimates*. Retrieved February 16, 2006 from http://www.dhss.mo.gov/profiles/Population/PopulationEstimatesDefinition.htm.

Prevalence ..... The proportion (usually the percentage) of a population that has a defined risk factor, disease, or condition, at a particular point in time. Although usually called a rate, it is actually a proportion.

Protocol ..... A written plan specifying the procedures to be followed in conducting research or an investigation.

Robust ..... The extent to which a statistical test yields essentially the same finding with a wide range of variations in performing the test. Related to statistical tests, robustness is a measure of a test's strength in handling data and data errors without test failure.

MSA ..... A Core Based Statistical Area associated with at least one urbanized area that has a population of at least 50,000. The Metropolitan Statistical Area (MSA) comprises the central county or counties containing the core, plus adjacent outlying counties having a high degree of social and economic integration with the central county as measured through community. Source: Federal Register / Vol. 65, No. 249 / Wednesday, December 27, 2000.

Standard Population ..... Standard population – a set of arbitrary population weights whose proportions are used as the standard in adjusting rates for different groups in order to eliminate differences between their rates which are based on their composition. The National Center for Health Statistics recommends that the projected U.S. 2000 standard population be used when calculating age-adjusted rates. However, if you compare rates from different sources, it is very important that you use the same standard population on both sides of your comparison. It is not legitimate to compare adjusted rates that use different standard populations. Source: Anderson RN, Rosenberg HM. Age Standardization of Death Rates: Implementation of the Year 2000 Standard. National vital statistics reports; vol 47 no.3. Hyattsville, Maryland: National Center for Health Statistics. 1998, found at: http://www.cdc.gov/nchs/data/nvsr/nvsr47/nvs47_03.pdf.
The following are the U.S. standard population distributions:

Age	2000 Proportion	Age	2000 Proportion
Under 1 year	0.013818	45 - 54 years	0.134834
1 - 4 years	0.055317	55 - 64 years	0.087247
5 - 14 years	0.145565	65 - 74 years	0.066037
15 - 24 years	0.138646	75 - 84 years	0.044842
25 - 34 years	0.135573	85 and over	0.015508
35 - 44 years	0.162613	All ages	1.000000

Standardized Rate ..... A standardized rate is a rate which has been adjusted for the effect of a confounding variable in order to obtain an undistorted view of the effect that other variables have on risk, as when comparing populations with different distributions of the potentially confounding variable. An age-adjusted rate is a commonly-used standardized rate. Source: Introduction to Public Health Surveillance Instructor's Guide (2003) Philip S. Brachman, MD, Kathleen R. Minor, PhD, MPH, CHES, Martha E. Alexander, MA, MPH, CHES, Tina-Lynn Paul, MPH, CHES, Lynn Eberhart, RN, MPH ,T. Demetri Vacalis, PhD, Altaf S. Musani, MPH http://www.cdc.gov/epo/surveillancein/inroduca.htm Accessed May 2006.

Statistically Significant ..... Describes a mathematical measure of difference between groups. The difference is said to be statistically significant if it is greater than what might be expected to happen by chance alone.

Rapid Case Ascertainment ..... The process of identifying new cancer cases currently not in existing databases. Reporting facility staff searches their records for new reportable cases and submits them to the central cancer registry.

Rate ..... A rate is a ratio of those having the public health event of interest (e.g., cancer) to the population of those at risk of having the given health event. Rates are calculated by dividing the number of events by the population at risk, or a related population, and then multiplying by a constant. The size of the constant depends on the rarity of the event being reviewed. Source: DHSS. *Rate*. Retrieved February 16, 2006 from http://www.dhss.mo.gov/GLRequest/MCHRate.html.

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